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### (54) OPIOID FORMULATIONS FOR TREATING PAIN

OPIOID-FORMULIERUNGEN ZUR SCHMERZBEHANDLUNG

FORMULATIONS D'OPIOIDES POUR LE TRAITEMENT DE LA DOULEUR

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**Description**

- [0001] The present invention relates to bioavailable sustained-release pharmaceutical formulations of analgesic drugs, in particular opioid analgesics, which provide an extended duration of effect when orally administered.
- 5 [0002] It is the intent of all sustained-release preparations to provide a longer period of pharmacologic response after the administration of the drug than is ordinarily experienced after the administration of the rapid release dosage forms. Such longer periods of response provide for many inherent therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. This is especially true in the treatment of cancer patients or other patients in need of treatment for the alleviation of moderate to severe pain, where blood levels of an opioid analgesic medicament must be maintained at a therapeutically effective level to provide pain relief. Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occur because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance of analgesic efficacy.
- 10 [0003] The prior art teaching of the preparation and use of compositions providing the sustained-release of an active compound from a carrier is basically concerned with the release of the active substance into the physiologic fluid of the alimentary tract. However, it is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability.
- 15 [0004] In order to be absorbed, the active drug substance must be in solution. The dissolution time required for a given proportion of an active substance from a unit dosage form is determined as the proportion of the amount of active drug substance released from a unit dosage form over a specified time base by a test method conducted under standardized conditions. The physiologic fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art recognizes many satisfactory test procedures to measure dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.
- 20 [0005] The primary principle guiding the use of opioid analgesics in the management of chronic pain is the individualization of dosages to meet the different and changing opioid requirements among and within each individual patient. Pain management authorities stress the importance of titration. Titration to the appropriate dose for a particular patient is necessitated by the wide inter-individual differences in the response of different patients to given doses of opioids. While a multitude of factors are responsible for wide inter-individual differences in the response to opioid analgesics, one important factor is rooted in the wide inter-individual variation in metabolism and pharmacokinetics.
- 25 [0006] Those opioids which are most efficiently titrated are those with relatively short elimination half-lives in the range of 3 to 5 hours (e.g., morphine, hydromorphone, oxycodone) as compared to long (12 to 72 hours) and more variable half-life analgesics (e.g., methadone, levorphanol). The shorter half life drugs approach steady-state concentrations in approximately a day rather than in several days to a week or more. Only at steady-state can one expect that the balance between efficacy and side effects will persist at a given dosing schedule. Having confidence that the patient is at approximate steady-state a day or so following initiation of dosing allows for much quicker assessment of whether the dosage is appropriate for that individual.
- 30 [0007] Once-a-day orally administrable dosage forms have previously been developed in the art and are commercially available. Presently, however, there are no commercially available sustained-release 24-hour opioid analgesic preparations; however, experience with the 12-hour sustained release preparations have led to a general understanding in the medical community that in order to titrate a patient who is to receive opioid analgesic therapy it is necessary to use an immediate release opioid analgesic dosage form, such as a parenteral formulation, an immediate release solution or tablet, or the like. Only after a suitable steady-state level is achieved in the patient by using immediate release opioid preparations may a patient be switched to a sustained release oral opioid formulation.
- 35 [0008] It therefore follows that it would be very desirable for practitioners to have available a sustained-release opioid analgesic preparation which provides appropriate pharmacokinetic parameters (e.g., absorption profile) and accompanying pharmacodynamic response in the patient (e.g., relief from pain) such that the same dosage form may be used to both titrate a patient receiving opioid analgesic therapy and used in chronic maintenance therapy after titration of the patient. This would eliminate the need to first titrate a patient on an immediate release opioid dosage form before switching the patient to a sustained-release dosage form for chronic therapy as described above. Preferably the sustained-release preparations will provide a duration of effect lasting longer than about twelve hours such that a drug that may be administered to a patient only once a day. Preferably, the sustained release dosage form will not only provide effective pain relief for a duration of greater than about 12 hours, but will additionally provide a pharmacokinetic and pharmacodynamic profile which will allow a patient who is to receive opioid analgesic therapy to be titrated and chronically treated with the same sustained-release dosage form.
- 40 [0009] Many of the oral opioid analgesic formulations that are currently available in the market must be administered every four to six hours daily; a selected few are formulated for less frequent 12 hour dosing.
- 45 [0010] There is also a need to develop a drug formulation which provides an absorption profile which is suitable for

both titrating a patient who is receiving opioid analgesic therapy and which also provides sustained release of an opioid analgesic sufficient to provide analgesia for at least about 12 hours duration. This would eliminate the need to first titrate a patient with immediate release dosage forms (e.g. parenteral, oral, rectal) of opioid analgesic and then switch the patient to a sustained release form of the opioid analgesic.

- 5 [0011] Morphine, which is considered to be the prototypic opioid analgesic, has been formulated into twice-daily controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Frederick company; and Kapanol®, commercially available from F.H. Faulding and company; and Oramorph® SR, previously referred to as Roxanol® SR, commercially available from Roxane). Reference is also made to PCT/WO 94/03161.
- 10 [0012] An orally administrable opioid formulation which would provide an extended duration of analgesia without higher incidence of adverse effects would be highly desirable. Such an oral sustained-release formulation of an opioid analgesic would be bioavailable and provide effective steady-state blood levels (e.g., plasma levels) of the drug when orally administered such that a duration of analgesic efficacy about 24 hours or more is obtained.

#### OBJECTS AND SUMMARY OF THE INVENTION

- 15 [0013] It is accordingly an object of the present invention to provide a method for treating patients in moderate to severe pain with an orally administered pharmaceutical dosage form of an opioid analgesic that is suitable for once-a-day administration.
- 20 [0014] It is yet another object of the present invention to provide a method for treating patients with a once-a-day opioid analgesic formulation which provides greater analgesic efficacy than that which is obtainable with the preferred Q12H (every 12 hour) analgesic therapies.
- [0015] It is further an object of the present invention to provide an opioid analgesic dosage form which provides sustained-release of the opioid and is also capable for use in titrating a patient receiving opioid analgesic therapy.
- 25 [0016] In accordance with the above objects and others, the present invention is related in part to the surprising discovery that in order to provide a 24 hour dosage form of an opioid analgesic, it is critical to formulate a sustained release formulation with an analgesic preparation which provides an initially rapid opioid release so that the minimum effective analgesic concentration can be quickly approached in many patients who have measurable if not significant pain at the time of dosing. Due to the unique release profile of the dosage form of the invention, it is possible to use a single dosage form according to the present invention to titrate a patient receiving opioid analgesic therapy while
- 30 providing sustained-release of an opioid analgesic to once-a-day sustained release oral dosage opioid formulations which comprise an opioid analgesic and an effective amount of at least one retardant material to cause the opioid analgesic to be released at an effective rate to provide an analgesic effect after oral administration to a human patient for at least about 24 hours. More particularly, the present invention provides an oral sustained release opioid formulation comprising:
- 35 a sustained release matrix including an opioid analgesic, which is tramadol or a salt thereof, and an effective amount of at least one retardant material to cause said opioid analgesic to be released at an effective rate to provide an analgesic effect after oral administration to a human patient for 24 hours, said retardant material selected from hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from 8 to 50 carbon atoms, polyalkylene glycols, said formulation when administered in humans providing an initially rapid rate of rise in the plasma concentration of said opioid characterized by providing an absorption half-life from 1 to 8 hours in the fasted state.
- 40 [0017] The inventive formulations, when administered in humans, provide an initially rapid rate of rise in the plasma concentration of the opioid characterized by providing an absorption half-life from 1.5 to about 8 hours. In preferred embodiments, the inventive once-daily oral sustained release formulations provides an absorption half-life from 2 to about 4 hours.
- 45 [0018] The present invention is also directed to a method for titrating human patients with a sustained release oral opioid formulation. The first step of this method comprises administering to a human patient on a once-a-day basis a unit dose of the inventive once-a-day oral sustained release opioid formulations described above and in the following paragraphs. Thereafter, the method includes the further step of monitoring pharmacokinetic and pharmacodynamic parameters elicited by said formulation in said human patient and determining whether said pharmacokinetic and/or pharmacodynamic parameters are appropriate to treat said patient on a repeated basis. The patient is titrated by adjusting the dose of said opioid analgesic administered to the patient by administering a unit dose of said sustained release opioid analgesic formulation containing a different amount of opioid analgesic if it is determined that said pharmacokinetic and/or said pharmacodynamic parameters are not satisfactory or maintaining the dose of said opioid analgesic in the unit dose at a previously administered amount if said pharmacokinetic and/or pharmacodynamic parameters are deemed appropriate. The titration is continued by further adjusting the dose of the opioid analgesic until appropriate steady-state pharmacokinetic/ pharmacodynamic parameters are achieved in the patient. Thereafter, the administration of the dose of the opioid analgesic in the oral sustained release formulation is continued on a once-a-

day basis until treatment is terminated.

[0019] The term "bioavailability" is defined for purposes of the present invention as the extent to which the drug (e.g., opioid analgesic) is absorbed from the unit dosage forms.

5 [0020] The term "sustained release" is defined for purposes of the present invention as the release of the drug (e.g., opioid analgesic) at such a rate that blood (e.g., plasma) levels are maintained within the therapeutic range but below toxic levels over a period of time of about 24 hours or longer.

[0021] The phrase "rapid rate of rise" with regard to opioid plasma concentration is defined for purposes of the present invention as signifying that the formulation provides a  $T_{1/2}$  (abs), or half-life of absorption, from 1.5 about hours to about 8 hours.

10 [0022] The term  $T_{1/2}$  (abs) is defined for purposes of the present invention as the amount of time necessary for one-half of the absorbable dose of opioid to be transferred to plasma. This value is calculated as a "true" value (which would take into account the effect of elimination processes), rather than an "apparent" absorption half-life.

15 [0023] The term "steady state" means that a plasma level for a given drug has been achieved and which is maintained with subsequent doses of the drug at a level which is at or above the minimum effective therapeutic level and is below the minimum toxic plasma level for a given drug. For opioid analgesics, the minimum effective therapeutic level will be partially determined by the amount of pain relief achieved in a given patient. It will be well understood by those skilled in the medical art that pain measurement is highly subjective and great individual variations may occur among patients.

20 [0024] The terms "maintenance therapy" and "chronic therapy" are defined for purposes of the present invention as the drug therapy administered to a patient after a patient is titrated with an opioid analgesic to a steady state as defined above.

#### DETAILED DESCRIPTION

[0025] Even at steady-state dosages of opioid analgesics, most patients remain in measurable or significant pain.

25 [0026] The state-of-the-art approach to controlled release opioid therapy is to provide formulations which exhibit zero order pharmacokinetics and have minimal peak to trough fluctuation in opioid levels with repeated dosing. This zero order release provides very slow opioid absorption, and a generally flat serum concentration curve over time. A flat serum concentration curve is generally considered to be advantageous because it would in effect mimic a steady-state level where efficacy is provided but side effects common to opioid analgesics are minimized. However, by formulating sustained release opioids in this manner, it has been discovered that the patients often experience considerable discomfort at about the time the next oral dose of the opioid is administered.

30 [0026] It has now been surprisingly discovered that quicker and greater analgesic efficacy is achieved by 24 hour oral opioid formulations which do not exhibit a substantially flat serum concentration curve, but which instead provide a more rapid initial opioid release so that the minimum effective analgesic concentration can be more quickly approached in many patients who have measurable if not significant pain at the time of dosing. Even at steady-state dosages of oral opioid analgesics, most patients have been found to remain in measurable or significant pain and would benefit greatly from treatment with the novel approach to oral opioid treatment disclosed herein. Also surprising and unexpected is the fact that while the methods of the present invention achieve quicker and greater analgesic efficacy, there is not a significantly greater incidence in side effects which would normally be expected as higher peak plasma concentrations occur.

35 [0027] Defining effective analgesic plasma opioid (e.g., morphine) levels is very complex. However, there is generally a "minimally effective analgesic concentration" (MEAC) in plasma for a particular opioid below which no analgesia is provided. While there is an indirect relationship between, e.g., plasma morphine levels and analgesia, higher plasma levels are generally associated with superior pain relief. There is a lag time or hysteresis, between the time of peak plasma opioid levels and the time of peak drug effects. This holds true for the treatment of pain with opioid analgesics in general.

40 [0028] The inventive sustained release once-a-day formulations may be characterized by the fact that they are designed to provide an initially rapid rate of rise in the plasma concentration of said opioid characterized by providing an absorption half-life from about 1 to about 8 hours, when the oral sustained release formulation is administered in the fasted state (i.e., without food). In certain embodiments, the absorption half-life is preferably from about 1 to about 6 hours, and more preferably from about 1 to about 3 hours.

45 [0029] The inventive formulations may be further characterized by having a surprisingly fast time to peak drug plasma concentration (i.e.,  $t_{max}$ ). The  $t_{max}$  of the sustained release formulations of the present invention may be from about 2 to about 10 Hours. In certain preferred embodiments, the  $t_{max}$  provided by these formulations may be from about 4 to about 9 hours.

50 [0030] The administration of 24-hour opioid oral sustained release formulations in accordance with the present invention reveals a greater degree of intensity of certain pharmacodynamic endpoints during the earlier portions of the plasma concentration curve (e.g., 4-8 hours after oral administration), such as sedation respiratory rate, pupil size,

and/or combined scores from a questionnaire of opioid effects reported by the subjects at serial times following each treatment (i.e., administration of the oral dosage form). Other measures of analgesic efficacy such as sum of pain intensity difference (SPID) and total pain relief (TOTPAR) have consistently higher numerical scores via the presently claimed methods, while also generating in many cases fewer adverse events (which in general are predominantly mild or moderate somnolence, nausea and/or dizziness). The opioid analgesic tramadol may be in the form of the free base or a salt.

[0031] The sustained release dosage forms of the present invention generally achieve and maintain therapeutic levels substantially without significant increases in the intensity and/or degree of concurrent side effects, such as nausea, vomiting or drowsiness, which are often associated with high blood levels of opioid analgesics. There is also evidence to suggest that the use of the present dosage forms leads to a reduced risk of drug addiction. Furthermore, the sustained release dosage forms of the present invention preferably releases the opioid analgesic at a rate that is independent of pH, e.g., between pH 1.6 and 7.2. In other words, the dosage forms of the present invention avoid "dose dumping" upon oral administration.

[0032] In the present invention, the oral opioid analgesics have been formulated to provide for an increased duration of analgesic action allowing once-daily dosing. Surprisingly, these formulations, at comparable daily dosages of conventional immediate release drug, are associated with a lower incidence in severity of adverse drug reactions and can also be administered at a lower daily dose than conventional oral medication while maintaining pain control.

[0033] The retardant material utilized in the sustained release formulations of the invention may be one which is known in the art, including but not limited to acrylic polymers, alkylcelluloses, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and mixtures of any of the foregoing.

[0034] The sustained release preparations of the present invention may be used in conjunction with any multiparticulate system, such as beads, spheroids, microspheres, seeds, pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained release of the therapeutically active agent. Beads, granules, spheroids, or pellets, prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage form.

[0035] When the substrates of the present invention are inert pharmaceutical beads, the inert pharmaceutical beads may be from about 8 mesh to about 50 mesh. In certain preferred embodiments, the beads are, e.g., nu parie 18/20 beads.

[0036] In some embodiments of the present invention, the present invention may utilize a multiparticulate sustained release matrix. Suitable materials for inclusion in a sustained release matrix are

(a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxy-alkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.

(b) Digestible, long chain ( $C_8C_{50}$ , especially  $C_{12}-C_{40}$ ), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

[0037] For example, a suitable matrix may be one which comprises at least one water soluble hydroxyalkyl cellulose, at least one  $C_{12}-C_{36}$ , preferably  $C_{14}-C_{22}$ , aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy ( $C_1$  to  $C_6$ ) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of opioid release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In certain preferred embodiments, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioid release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

[0038] In one embodiment, the ratio of, e.g., at least one hydroxyalkyl cellulose or acrylic resin to at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid from the formulation. A ratio of the at least one hydroxyalkyl cellulose to at least one aliphatic alcohol/ polyalkylene glycol of between 1:2 and

1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

[0039] At least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

5 [0040] Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol and, optionally, a polyalkylene glycol.

[0041] In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

10 [0042] These sustained release matrices may be prepared, for example, by

- (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and opioid or an opioid salt,
- (b) mixing the hydroxyalkyl cellulose containing granules with at least one C<sub>12</sub>-C<sub>36</sub> aliphatic alcohol, and
- 15 (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/opioid with water. The amount of water added during the wet granulation step may be, e.g., between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid.

[0043] In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred, although hydrous lactose impalpable is preferably utilized for morphine sulfate sustained release formulations prepared by powder-layering techniques. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

[0044] The substrates of the present invention may also be prepared via a melt pellitization technique. In such circumstance, the opioid in finely divided form is combined with a binder (also in particulate form) and other optional inert ingredients, and thereafter the mixture is pelletized, e.g., by mechanically working the mixture in a high shear mixer to form the pellets (granules, spheres). Thereafter, the pellets (granules, spheres) may be sieved in order to obtain pellets of the requisite size. The binder material is preferably in particulate form and has a melting point above about 40° C. Suitable binder substances include, for example, hydrogenated castor oil, hydrogenated vegetable oil, other hydrogenated fats, fatty alcohols, fatty acid esters and fatty acid glycerides.

[0045] In certain preferred embodiments of the present invention, an effective amount of opioid in immediate release form is included in the 24 hour sustained release unit dose opioid formulation to be administered. The immediate release form of the opioid is included in an amount which is effective to shorten the time to maximum concentration of the opioid in the blood (e.g., plasma). In such embodiments, an effective amount of the opioid in immediate release form may be coated onto the substrates of the present invention. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the opioid is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising a effective unit dose of the opioid (e.g., multiparticulate systems including pellets, spheres or beads) are incorporated into a hard gelatin capsule, the immediate release portion of the opioid dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release opioid as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the opioid. One skilled in the art would recognize still other alternative manners of incorporating the immediate release opioid portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims. It has been discovered that by including such an effective amount of immediate release opioid in the unit dose, the experience of relatively higher levels of pain in patients is significantly reduced.

50 [0046] The dosage form may be provided by preparing a dosage form consistent with one of the above described methods or by other means known to those skilled in the pharmaceutical art.

[0047] In addition to the above, the sustained release opioid formulations may also be manufactured as tablets. In such instances, the tablet may contain, in addition to the opioid and the retardant material, suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986). Techniques and compositions for making solid oral dosage forms are described in Pharmaceutical Dosage Forms: Tablets (Lieberman,

Lachman and Schwartz, editors) Second Edition, published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

[0048] In order to titrate a human patient with the inventive sustained release opioid formulations, a plurality of blood samples are taken from the patient over the course of the dosing interval. The samples thus obtained are then tested to determine the plasma level of the opioid analgesic, and any active metabolites thereof. The values thus obtained may then be utilized to determine additional pharmacokinetic parameters. A determination as to whether the patient has obtained an adequate pharmacodynamic response with said dosage form will be made, e.g., reference to predetermined blood levels, comparison of the results subjective pain tests given to the patient, the adverse effect profile of the drug in the patient, or the like. A determination may then be made as to whether an upward or downward adjustment of the dose is necessary.

[0049] The administration of the sustained release unit dosage form is continued over the dosing interval of the unit dose to maintain an adequate pharmacodynamic response with the sustained release dosage form. Preferably the adequate pharmacodynamic response will last between about 12 and about 24 hours, most preferably about 24 hours or greater.

[0050] The administration of the sustained release unit dosage form is continued over the dosing interval of the unit dose to maintain said adequate pharmacodynamic response with said sustained release dosage form.

[0051] If necessary, the above steps are repeated until a determination of adequate pharmacodynamic response is obtained with the sustained release unit dosage form.

[0052] According to the above method, a patient may be titrated with a sustained release opioid analgesic dosage form. Subsequent maintenance therapy may be provided with the same sustained release dosage form.

#### Reference Example

[0053] The following example is provided as a reference example to illustrate the principles underlying the present invention when applied to other drugs.

#### EXAMPLE 1

##### Matrix Beads

[0054] Matrix Beads with a higher loading of morphine sulfate were produced with the use of the powder layering technique in the Glatt Rotor Processor. The formulation of the high load matrix beads is set forth in Table 1 below.

TABLE 1

Ingredient	High Load Bead mg/unit	Percent (%)
Morphine Sulfate Powder	60.0 mg	46.0%
Lactose	12.0 mg	9.2%
Eudragit RS30D	29.10 mg	22.4%
Povidone C-30	5.80 mg	4.5%
Sugar Beads	16.80 mg	12.9%
Opadry	6.50 mg	5.0%
Purified Water	gs	---
Total	130.20 mg	100%

[0055] The matrix component is comprised of an ethylcellulose polymer (i.e., Aquacoat ECD 30). A HPMC protective coat was also included after the aquacoat layer to further enhance stability.

[0056] The matrix beads were made as follows. The Aquacoat ECD 30 was plasticized with tributyl citrate for approximately 30 minutes. Morphine sulfate powder and lactose were blended for approximately 5 minutes in a hobart mixer. A load of sugar beads was charged into the rotor insert of a Glatt equipped with a 1.2 mm spray nozzle/powder feed assembly. An Accurate Powder Feeder was positioned over the spray nozzle/powder feed assembly and charged with the morphine sulfate/lactose blend. The morphine sulfate/lactose blend is then layered onto the sugar beads using the plasticized hydrophobic polymer dispersion (i.e., Aquacoat ECD 30 and tributyl citrate) as the binding agent. Upon completion of the layering process the final protective Opadry dispersion overcoat was then applied. The beads were then cured for one day in a dry oven of 60°C. The cured beads were then filled into gelatin capsules at a 60 mg strength.

[0057] The capsules were then subjected to dissolution testing. Dissolution testing was conducted on the finished products via USP Apparatus II-(Paddle Method). The capsules were placed into 700 ml of simulated gastric fluid (without enzymes) for the first hour at 100 rpm and 37°C, and then placed into 900 ml of simulated intestinal fluid (without enzymes) after the first hour. The results of dissolution testing is set forth in Table 2 below.

5

TABLE 2

Time	% Morphine Sulfate Dissolved
1 hour	32.4%
2 hours	44.8%
4 hours	59.6%
8 hours	76.6%
12 hours	88.0%
18 hours	97.6%
24 hours	102.2%

CLINICAL EVALUATION OF EXAMPLE 1

[0058] Normal healthy human subjects were enrolled in a crossover, randomized, open label study assessing the effect of food on the pharmacokinetics and pharmacodynamics of a single dose of example 1, with or without food. Plasma samples were analyzed for morphine levels and the following pharmacokinetic results were calculated, and the results are set forth in Table 3 below.

25

TABLE 3

Example Number	Pharmacokinetic Parameter Per 60 mg Dose		
	AUC (ng/ml.hr)	Cmax (ng/ml)	Tmax (hours)
1 Fasted	154	14.3	1.8
1 Fed	154	12.7	2.8

**Claims**

35

1. An oral sustained release opioid formulation comprising:  
a sustained release matrix including an opioid analgesic, which is tramadol or a salt thereof, and an effective amount of at least one retardant material to cause said opioid analgesic to be released at an effective rate to provide an analgesic effect after oral administration to a human patient for 24 hours, said retardant material selected from hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from 8 to 50 carbon atoms, polyalkylene glycols, said formulation when administered in humans providing an initially rapid rate of rise in the plasma concentration of said opioid characterized by providing an absorption half-life from 1 to 8 hours in the fasted state.
2. The sustained release formulation of claim 1, wherein said oral sustained release provides an absorption half-life from 1 to 6 hours.
3. The sustained release formulation of claim 1, wherein said oral sustained release provides an absorption half-life from 1 to 3 hours.
4. The sustained release formulation of claims 1 to 3, which provides a peak plasma level of said opioid in-vivo from 2 to 10 hours after administration.
5. The sustained release formulation of claims 1 to 4, which comprise a plurality of substrates including said opioid, each of said substrates having a diameter from 0.1 mm to 3 mm.
6. The sustained release formulation of claim 1 to 5, wherein said retardant material is an acrylic resin.

7. The sustained release formulation of claim 1 to 5, wherein said retardant material is alkylcellulose, preferably ethylcellulose.
- 5 8. The sustained release formulation of claim 1 to 5, wherein said digestible substituted or unsubstituted hydrocarbons of said retardant material are selected from the group consisting of fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral oils, vegetable oils, waxes, and mixtures thereof.
- 10 9. The sustained release formulation of claim 8, wherein said fatty alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, and stearyl alcohol.
- 15 10. The sustained release formulation of claim 1 to 5, wherein said retardant material is selected from the group consisting of acrylic polymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures of any of the foregoing.
12. The sustained release formulations of claims 1 to 10, wherein a portion of the dose of said opioid is included in said formulation in immediate release form by coating said controlled release matrix with a portion of the dose of said opioid.
- 20 12. The sustained release formulation of claims 1 to 5, which is in the form of a tablet.

#### Patentansprüche

1. Orale Depot-Opioid-Formulierung, umfassend:
  - 25 eine Depotmatrix, einschließend ein Opioid-Analgetikum, welches Tramadol oder ein Salz davon ist, und eine wirksame Menge mindestens eines Verzögerungsmaterials, um zu bewirken, daß das Opioid-Analgetikum mit einer wirksamen Geschwindigkeit freigesetzt wird, um nach oraler Verabreichung an einen menschlichen Patienten für 24 Stunden eine analgetische Wirkung bereitzustellen, wobei das Verzögerungsmaterial aus hydrophilen Polymeren, hydrophoben Polymeren, verdaulichen substituierten oder unsubstituierten Kohlenwasserstoffen mit 8 bis 50 Kohlenstoffatomen, Polyalkylenglyolen ausgewählt ist, wobei die Formulierung, wenn verabreicht an Menschen, eine anfänglich schnelle Geschwindigkeit des Anstiegs der Plasmakonzentration des Opioids, gekennzeichnet durch Bereitstellen einer Halbwertszeit der Absorption von 1 bis 8 Stunden im Fastenzustand, bereitstellt.
  - 30 2. Depotformulierung nach Anspruch 1, wobei das orale Depot eine Halbwertszeit der Absorption von 1 bis 6 Stunden bereitstellt.
  - 35 3. Depotformulierung nach Anspruch 1, wobei das orale Depot eine Halbwertszeit der Absorption von 1 bis 3 Stunden bereitstellt.
  - 40 4. Depotformulierung nach den Ansprüchen 1 bis 3, welche ein Spitzenplasmaniveau des Opioids in vivo von 2 bis 10 Stunden nach der Verabreichung bereitstellt.
  5. Depotformulierung nach den Ansprüchen 1 bis 4, welche eine Mehrzahl von Substraten einschließlich des Opioids umfaßt, wobei jedes der Substrate einen Durchmesser von 0,1 mm bis 3 mm hat.
  - 45 6. Depotformulierung nach Anspruch 1 bis 5, wobei das Verzögerungsmaterial ein Acrylharz ist.
  7. Depotformulierung nach Anspruch 1 bis 5, wobei das Verzögerungsmaterial Alkylcellulose, vorzugsweise Ethylcellulose, ist.
  - 50 8. Depotformulierung nach Anspruch 1 bis 5, wobei die verdaulichen substituierten oder unsubstituierten Kohlenwasserstoffe des Verzögerungsmaterials aus der Gruppe, bestehend aus Fettsäuren, Fettalkoholen, Glycerylestern von Fettsäuren, Mineralölen, Pflanzenölen, Wachsen und Gemischen davon, ausgewählt sind.
  - 55 9. Depotformulierung nach Anspruch 8, wobei der Fettalkohol aus der Gruppe, bestehend aus Laurylalkohol, Myristylalkohol und Stearylalkohol, ausgewählt ist.
  10. Depotformulierung nach Anspruch 1 bis 5, wobei das Verzögerungsmaterial aus der Gruppe, bestehend aus Acryl-

polymeren, Schellack, Zein, hydriertem Castoröl, hydriertem Pflanzenöl und Gemischen von jedem der vorhergehenden, ausgewählt ist

- 5        11. Depotformulierungen nach den Ansprüchen 1 bis 10, wobei ein Anteil der Dosis des Opioids in die Zubereitung in einer Form zu sofortiger Freisetzung eingeschlossen wird, indem die Matrix zur gesteuerten Freisetzung mit einem Anteil der Dosis des Opioids beschichtet wird.
- 10      12. Depotformulierung nach den Ansprüchen 1 bis 5, welche in der Form einer Tablette ist.

10      **Revendications**

1. Formulation d'opioïde à libération orale prolongée comprenant :  
une matrice de libération prolongée comprenant un analgésique opioïde, qui est le tramadol ou un de ses sels, et une quantité efficace d'au moins une substance retardante pour amener ledit analgésique opioïde à être libéré à une vitesse efficace pour assurer un effet analgésique après administration orale à un patient humain pendant 24 heures, ladite substance retardante étant choisie parmi les polymères hydrophiles, les polymères hydrophobes, les hydrocarbures digestibles substitués ou non substitués ayant 8 à 50 atomes de carbone, les polyalkylèneglycols, ladite formulation une fois administrée à des humains donnant une vitesse initialement rapide d'élévation de la concentration plasmatique dudit opioïde **caractérisée par le fait de donner une demi-vie d'absorption de 1 à 8 heures à l'état à jeun.**
2. Formulation à libération prolongée de la revendication 1, dans laquelle ladite libération orale prolongée donne une demi-vie d'absorption de 1 à 6 heures.
3. Formulation à libération prolongée de la revendication 1, dans laquelle ladite libération orale prolongée donne une demi-vie d'absorption de 1 à 3 heures.
4. Formulation à libération prolongée des revendications 1 à 3, qui donne un taux plasmatique maximal dudit opioïde *in vivo* 2 à 10 heures après administration.
5. Formulation à libération prolongée des revendications 1 à 4, qui comprend une pluralité de substrats comprenant ledit opioïde, chacun desdits substrats ayant un diamètre de 0,1 mm à 3 mm.
- 35     6. Formulation à libération prolongée des revendications 1 à 5, dans laquelle ladite substance retardante est une résine acrylique.
7. Formulation à libération prolongée des revendications 1 à 5, dans laquelle ladite substance retardante est une alkylcellulose, de préférence l'éthylcellulose.
- 40     8. Formulation à libération prolongée des revendications 1 à 5, dans laquelle lesdits hydrocarbures digestibles substitués ou non substitués de ladite substance retardante sont choisis dans le groupe constitué des acides gras, des alcools gras, des esters de glycéryle d'acides gras, des huiles minérales, des huiles végétales, des cires, et de leurs mélanges.
- 45     9. Formulation à libération prolongée de la revendication 8, dans laquelle ledit alcool gras est choisi dans le groupe constitué de l'alcool laurylique, de l'alcool myristylique, et de l'alcool stéarylique.
- 50     10. Formulation à libération prolongée des revendications 1 à 5, dans laquelle ladite substance retardante est choisie dans le groupe constitué des polymères acryliques, de la gomme laque, de la zéine, de l'huile de ricin hydrogénée, de l'huile végétale hydrogénée, et des mélanges de n'importe lesquels des précédents.
- 55     11. Formulation à libération prolongée des revendications 1 à 10, dans laquelle une partie de la dose dudit opioïde est incorporée dans ladite formulation sous une forme à libération immédiate par enrobage de ladite matrice de libération contrôlée avec une partie de la dose dudit opioïde.
12. Formulation à libération prolongée des revendications 1 à 5, qui est sous la forme d'un comprimé.